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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,862	06/19/2007	Nils Griebenow	BHC 031071	4070

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Barbara A. Shimei
Director, Patents & Licensing
Bayer HealthCare LLC - Pharmaceuticals
555 White Plains Road, Third Floor
Tarrytown, NY 10591

EXAMINER	
KLINKEL, KORTNEY L	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,862	GRIEBENOW ET AL.	
	Examiner	Art Unit	
	Kortney Klinkel	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-14* is/are pending in the application.

4a) Of the above claim(s) *5,7 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims

Claims 1-5, and 7-14 are pending in the instant Office action.

Election/Restriction

Applicant's election with traverse of Group I, claim 1-4 and 8-9 in the reply filed on June 13, 2008 is acknowledged. The traversal is on the ground(s) that the examination of the compounds and their related methods of use would likely be co-extensive and, in any even, would involve such interrelated art that the search and examination of both groups could be made without undue burden on the Examiner. This is not found persuasive because the establishment of burden on the Office applies to US cases only. The instant application is a national stage entry of an international application under 35 U.S.C. 371. As a result, lack of unity practice is observed for restriction purposes.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4 and 8-9 are under consideration in the instant Office action.

Information Disclosure Statement

Acknowledgement is made of applicant's submitting an information disclosure statement on August 9, 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Foreign Priority

Acknowledgement is made of applicant's foreign priority claim to German patent application serial number 102004006325.7 filed February 10, 2004. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I) and (IA) and salts thereof, does not reasonably provide enablement for solvates or solvates of salts of compounds of formula (I) or (IA). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or

use the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

All of these factors have been considered with the most relevant ones discusses below.

The nature of the invention and the breadth of the claims. The nature of the invention is the compounds in instant Claims 1-4 or a salt, solvate or solvate of a salt thereof, further comprising a pharmaceutical composition which comprises a pharmaceutically suitable excipient (claim 9) or a further active ingredient (claim 8). The invention is complex in that these claims encompass novel compositions of matter. The instant breadth of the rejected claims immense. Specifically; the instant claims include *any* solvate of the claimed compounds *and any* solvate of *any* salt (pharmaceutically acceptable or not) of the claimed compounds. Claim 9 further includes the combination

of these multiple forms of formula (I) with a second active ingredient. The breadth of the claims exacerbates the complexity of the invention. In the present case, the great breadth of the claims means that the invention encompasses very dissimilar elements that are structurally and functionally distinct. The claims are extremely broad in that they encompass a large genus of compounds and compositions of matter.

The state of the prior art and the predictability or lack thereof in the art. Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties. Furthermore, these different polymorphs (solvates, hydrates, salts and/or solvates of salts) can have different and unpredictable reactivity/stability when in combination with further active ingredients.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization Morissette et al. ("High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids" Advanced Drug Delivery Reviews 2004, 56, 275-300). For these reasons, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorphs, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. It is therefore desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" Vippagunta et al. ("Crystalline solids" Advanced Drug Delivery Reviews, 2001, 48, 3-26, specifically see the abstract). In further discussing the predictability of the formation of solvates, Vippagunta disclose that "predicting the formation of solvates or hydrates of a

compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

The amount of direction or guidance present and the presence or absence of working examples. The only direction or guidance present in the instant specification is for compounds of claims 1-4. There is no data present in the specification for the preparation of salts, solvates or solvates of salts of the compounds of claim 1. The specification is silent as to the presence of any salts, solvates or solvates of salts. Additionally, preferred embodiments and examples do not support enablement for salts, solvates or solvates of salts of the disclosed compounds. Finally, there are no working examples present in the disclosure for the preparation of salts, solvates or solvates of salts. In each of the working examples, the compound was isolated from solution, resulting in the original compound, as a solid, not a solvated form.

The quantity of experimentation needed. Given the complexity of the invention, the large genus of compounds encompassed by the claims, the lack of specific guidance with regard to which compounds or salts, solvates or solvates of salts of the compounds will retain functional activity, and the lack of predictability in the art with respect to solvates, it will require undue and unpredictable experimentation in order to make and use the recited compounds, salts, solvates or solvates of salts and subsequent pharmaceutical formulations.

Genetech Inc. V. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compounds or salts, solvates or solvates of salts assert functionality appropriate for cosmetic compositions, with no assurance of success. Thus, rejection of claims 1-4 and 8-9 under 35 U.S.C. §112, first paragraph, is deemed proper.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

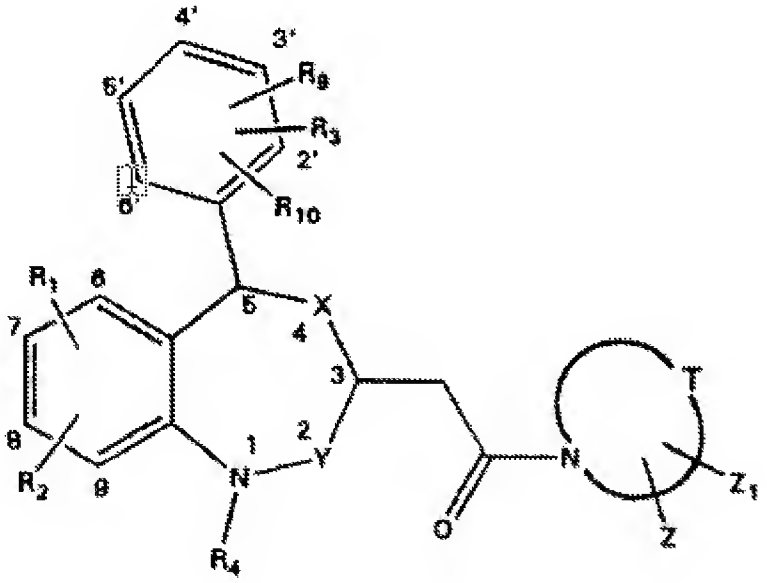
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamanaka et al. (WO 97/48701) in further view of Pandit et al. (Journal of Biological Chemistry, "Crystal Structure of Human Squalene Synthase" vol. 275(39) 2000, 30610-30617).

Hamanaka teach compounds of the following general structure for use as squalene synthetase inhibitors for use in pharmaceutical compositions (claim 1, also page 1, lines 1-6). Claim 1 describes the definitions of the variables.



Hamanaka also teaches the combination of the compounds of the above formula with additional active ingredients including other cholesterol synthesis inhibitors and cholesterol absorption inhibitors (page 49 lines 4-9).

The teachings of Hamanaka differ from the instant invention in that the compounds of Hamanaka are structural isomers of those recited in the instant invention. Both Hamanaka's compounds and the instant compounds contain the same functionality off the 5-, 3- 2- and 1-positions of the 7-memebered ring, the only difference being the location of the nitrogen atom and the presence of an oxo group in the 4-position of Hamanaka's compounds. Both sets of compounds also comprise a benzene ring moiety connected to the 7-membered ring system that can be optionally substituted. Hamanaka's compounds and the instant compounds are three-dimensionally very similar. The data provided in the instant specification states that the instant compounds, like those of Hamanaka are squalene synthetase inhibitors with an IC_{50} value of at least 20 μM (page 80, line 27).

Pandit teaches the crystal structure of human squalene synthase. The crystal structure of the protein with three different inhibitor complexes is described (page 30614, final paragraph and figures 6 a-c). The inhibitors of figures 6a and 6c, CP-320473 and CP-424677 respectively show IC_{50} values of 56 and 32 nM respectively. The inhibitor of figure 6b, CP-458003, an analog of CP-320473, is smaller and thus fills a smaller portion of the binding pocket and as a result is less potent and shows IC_{50} values around 30 μM, much like the instant compounds. Pandit teaches that the inhibitor binding pockets are largely hydrophobic and have the ability to change size and

shape in order to accommodate different ligands. This shape change is accomplished through rotations of the Phe^{54} and Tyr^{73} side chains as well as through backbone rotations (page 30616, fig. 6 description, also the final portion of the second paragraph of the second column on page 30616).

With the knowledge that structurally similar 7-membered ring compounds taught by both Hamanaka and Pandit show squalene synthase inhibition along with the fact that the squalene synthase binding pocket is non-discriminatory, it would have been prima facie obvious to the ordinarily skilled artisan at the time of the instant invention to arrive at the compounds of the instant invention with a reasonable expectation for success.

Applicant's data in the specification, as eluted to above, has been considered. All 53 exemplary embodiments, despite vastly different substitutions, exhibit IC_{50} values of less than 20 μM. This finding is consistent with the teachings of Pandit, namely that the inhibition binding pocket is flexible and therefore relatively non-discriminatory. One would expect three-dimensionally similar compounds to exhibit similar inhibition in this system.

Conclusion

Claims 1-4 and 8-9 are rejected. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel, Ph.D. whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 8am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached at (571)272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615